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Adiponectin as a Predictor for the Severity of Sepsis in ICU Patients

Thesis

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List of Abbreviations

ADM	Adrenomedullin
AF	Atrial fibrillation
AIDS	Acute immunodeficiency syndrome
ALI	Acute lung injury
ALT	Alanine aminotransferase
ANP	Atrial natriuretic peptide
APACHE	Acute Physiology and Chronic Health Evaluation
APN	Adiponectin
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
BMI	Body mass index
BW	Body weight
CAD	Coronary artery disease
CA-UTI	Community-acquired urinary tract infections
CBC	Complete blood count
CIMT	Common carotid artery intima-media thickness
CLD	Chronic liver disease
CLP	cecal ligation and puncture
COX	Cyclooxygenase
CRP	C-Reactive Protein
CT	Computerized tomography
CVP	Central venous pressure
dC	Delta change
DIC	Disseminated intravascular coagulation

EC	Endothelial cells
ED	Emergency department
EEG	Electroencephalographic
ELISA	Enzyme-linked immunosorbent assay
eNOS	Endothelial nitric oxide synthase
ERK	Extracellular signal-regulated kinase
FIO_2	Fraction of oxygen in the gases inspired
GCS	Glasgow Coma Score
GI	Gastrointestinal
GU	Genitourinary
HDL	High density lipoprotein
HR	Heart rate
HRP	Horseradish peroxidase
HS	Highly significant
ICAM	Intercellular adhesion molecule
ICU	Intensive care unit
IFN-γ	Interferon-γ
IL	Interleukin
INR	international normalized ratio
KO	Knockout
LDL	Low density lipoprotein
LPS	Lipopolysaccharide
LV	Left ventricle
MAP	Mean arterial press
MCP	Monocyte chemo attractant protein
MI	Myocardial infarction
MICs	Minimum inhibitory concentrations
MIF	Macrophage migration inhibitory factor

MMP	Metalloproteinases
MODS	Multiple organ dysfunction syndrome
MRI	Magnetic resonance imaging
MRSA	Methicillin-resistant Staphylococcus aureus
NAFLD	non-alcoholic fatty liver disease
NIV	Noninvasive ventilation
NO	Nitric oxide
NS	Non-significant
OF	Organ failures
oxLDL	Oxidized low-density lipoprotein
$PaCO_2$	Arterial partial-pressure of carbon dioxide
PACs	Pulmonary artery catheters
PAD	Percutaneous abscess drainage
PAF	Platelet-activating factor
PAI-1	Plasminogen activator inhibitor-1
PaO_2	Arterial partial-pressure of oxygen
PCR	Polymerase chain reaction
PCT	Procalcitonin
PEEP	Positive end-expiratory pressure
PI3-kinase	Phosphatidylinositol 3 kinase
PIRO	Predisposition, insult/infection, response, and organ dysfunction
PLA2	Phospholipase A2
PLA2	Phospholipase A2
PPAR	Peroxisome-proliferator-activated receptor
PPAR gamma	peroxisome proliferator-activated receptor gamma

PPARg	Peroxisome proliferator-activated receptor gamma
P-value	Probability value
RBC	Red blood cells
RR	Respiratory rate
RV	Right ventricle
S	Significant
SDD	Selective Digestive Tract Decontamination
SIRS	Systemic inflammatory response syndrome
SNP	Single nucleotide polymorphism
sTREM	Soluble Triggering Receptor Expressed on Myeloid Cells
SUP	Stress Ulcer Prophylaxis
TBRI	Theodor Bilharz Research Institute
TF	Tissue factor
TIMP	Metalloproteinases
TLRs	Toll-like receptors
TMB	Tetramethyl Benzidine
TNF	Tumour necrosis factor
TREM-1	Triggering receptor expressed on myeloid cells 1
TTE	Transthoracic echocardiographic
UFH	Unfractionated heparin
VAP	Ventilator-associated pneumonia
VCAM	Vascular cell adhesion molecule
WBC	White blood cell
WT	Wild Type

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Mohammed Amin Abdel Ghany

Introduction

Sepsis, defined by consensus conference as "the systemic inflammatory response syndrome that occurs during infection," ***(Almog et al., 2004), (Neviere, 2012)).*** The statistics related to the incidence of sepsis are striking. The reported rates of severe sepsis average around 10 cases per 100 intensive care unit (ICU) admissions ***(Linde-Zwirble and Angus, 2004).***

A number of risk factors exist for the development and progression of sepsis, including advanced age, compromised immune system response, chronic illness, broad-spectrum antibiotic use, and exposure to infection risk associated with surgical and invasive procedures ***(Hotchkiss and Karl, 2003).*** Identified risk factors for mortality in sepsis include the microbiological etiology of sepsis, the site of infection, with increased mortality associated with intraabdominal or lower respiratory tract infections, presence of underlying disease, source and type of infection, presence of shock, need for vasopressors, multiple organ failure, and neutropenia ***(Angus and Wax, 2001).***

The inflammatory response is a central component of sepsis as it drives the physiological alterations that are recognized as the SIRS ***(Remick, 2005).***

A successful inflammatory response eliminates the invading microorganisms without causing lasting damage.

Sepsis develops when the initial, appropriate host response to an infection becomes amplified, and then aberrant. Bacterial components reacting with specific toll receptors are believed to trigger monocytes, neutrophils, and endothelial cells (EC) to initiate an inflammatory cascade ***(Modlin et al., 1999) and (Reinhart et al., 2005).*** Many believe that sepsis develops as a result of exuberant production of proinflammatory molecules such as TNF-α and IL-1, IL-6, and IL-8, lysosomal enzymes, superoxide-derived free radicals, vasoactive substances, such as platelet-activating factor (PAF), tissue factor (TF), and plasminogen activator inhibitor-1 (PAI-1) ***(Andrews et al., 2007).*** This occurs in conjunction with increases in the expression of inducible nitric oxide (NO) synthase, increasing production of NO resulting in coagulopathy, endothelial dysfunction, vascular instability, and eventually to apoptosis (i.e. programmed cell death) and multi-organ failure.

Given the complexity of sepsis syndrome, merely blocking a single component; (for example, TNF-α and IL-1) may be insufficient to arrest the inflammatory process ***(Marshall, 2003) and (Glauser, 2000).*** Consideration needs to be given to modulation of multiple targets which are central to the pathophysiological response in sepsis. Where activation of a critical part of the inflammatory pathway exhibits multiple or redundant pathways, we may need to intervene at two or more drivers of the process ***(Sabroe, 2007).*** Therefore, future strategies of intervention which modify several arms of the

inflammatory cascade may possibly be more successful ***(Mekontso-Dessap et al., 2006).***

A marker of sepsis has been defined as "a measure that identifies a normal biologic state or that predicts the presence or severity of a pathologic process or disease." ***(American College of Chest Physicians, 1992)***. C-Reactive Protein (CRP) is an acute-phase protein released by the liver after the onset of inflammation or tissue damage. Some studies show the value of CRP as marker of infection or sepsis ***(American College of Chest Physicians, 1992)***. Procalcitonin has been recently studied as a possible marker of sepsis with a superior sensitivity and specificity, comparing with other markers ***(Meisner, et al., 1999).*** Among pro-inflammatory cytokines IL-6 and IL-8 are most closely related to the severity of the sepsis ***(Pinsky, 1993),*** particularly high levels of IL-6 were found in non-surviving septic patients. Other cytokines, such as TNF-, IL-1 or IL-10 showed poor correlation with the clinical course of sepsis ***(Pinsky, 1993)***. TNF - receptor antagonist (TNF-RA), Phospholipase A2 (PLA2), Neutrophil elastase, HLA-DR, CD64, Soluble Triggering Receptor Expressed on Myeloid Cells (sTREM), Macrophage migration inhibitory factor (MIF) all are elevated in patients with sepsis ***(Gibot et al., 2005).***

The normal blood lactate concentration in unstressed patients is 0.5-1 mmol/L. Patients with critical illness can be considered to have normal lactate concentrations of less than 2 mmol/L. Hyperlactatemia is defined as a mild-to-moderate